DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Jerome J. Klawitter, Ph.D.
President and CEO
Ascension Orthopedics, Inc.
8200 Cameron Road, Suite C-140
Austin, Texas 78754

MAY 1 2001

Re: P000057
Ascension® MCP
Filed: February 20, 2001
Amended: February 20, 2001 and March 16, 2001

Dear Dr. Klawitter:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA) including Amendments 1 and 2. We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

Because of the lack of information described below, review of the PMA cannot continue until the deficiencies listed in this letter have been addressed.

Your primary effectiveness endpoint was implant survival as defined by removal for any reason. An offset value, or delta, of 10% was chosen, which meant that the 10-year survival for the pyrolytic carbon joint prosthesis group could be up to 10 percentage points less than the Swanson Silastic joint prosthesis group before it would be considered statistically inferior. Please note that the pyrolytic carbon joint prosthesis was the implant used in the retrospective study while the Ascension MCP is the device for which you have requested a marketing application. Using the survival curve in the literature article by Hansraj and co-workers, 1997, the 10-year survival for the Swanson Silastic joint prosthesis was 90.3%. The 10-year survival for the pyrolytic carbon joint prosthesis was 84.3%. When these results were compared statistically, treating the limited amount of control data collected by Hansraj as a historical control with variance, the p-value was 0.2032. This value is much higher than the p=0.05 convention for statistical significance. Therefore, as discussed in our meeting on March 29, 2001, we believe that you have not demonstrated that the pyrolytic carbon joint prosthesis is non-inferior to the Swanson Silastic joint prosthesis with respect to your primary effectiveness endpoint.

In addition, from our review of 20 applicable literature articles you provided, including the Hansraj article, it appeared as if the researchers evaluated the following effectiveness endpoints

in addition to implant survival in there determination of patient and implant success and failure: range of motion, pain, function, strength (grip and pinch), deformity, patient satisfaction, flexion, extension, and radiographic information. We also believe that these types of endpoints including pain, function (finger joint and hand), and radiographic data should be considered primary effectiveness endpoints in addition to implant survival. From our review of the summary information in the patient case histories, it appeared as if there were several patients who were described as in severe pain, unable to grip, had very limited function, or had hands that were "useless" but who did not have the pyrolytic carbon joint prosthesis removed. Although these patients did not have their study implants removed, with the limited amount of information presented for these patients in the case histories, we would not consider these types of outcomes successful. In your PMA, you collected and presented this information as secondary effectiveness endpoints. However, rather than defining effectiveness in terms of individual patient and implant success and failure criteria incorporating the primary and secondary effectiveness endpoints, you compared the study and control means for each secondary endpoint separately. With each secondary endpoint presented and analyzed separately, the amount of information was limited and made it difficult to draw conclusions about the effectiveness of the subject device as compared to a historical control.

In Table 3 of Amendment 1, you summarized study population follow-up information for what you identified as "key" secondary effectiveness endpoints. In the column labeled ">18 months," follow-up rates for these endpoints were as follows: range of motion, 49% (20/41 patients); ulnar deviation, 12% (5/41 patients); joint position (i.e., reduction, subluxation, dislocation), 68% (28/41 patients); strength (pinch or grip), 34% (14/41 patients); patient activity level, 76% (31/41 patients); cosmesis, 22% (5/41 patients); patient satisfaction, 61% (25/41 patients); and pain improvement, 88% (36/41 patients). Please note that for total joint replacement devices, we typically request a minimum of 2 years of follow-up data on each patient before safety and effectiveness are evaluated. Because of the lack of follow-up data for these "key" secondary effectiveness endpoints, there is no way to know that the data presented is representative of the entire patient population. Therefore, your subsequent statistical analysis, presented in Amendment 2, in which you compared the subject and control devices with respect to these secondary endpoints may have contained patient selection bias.

In addition, rather than defining safety in terms of individual patient and implant success and failure, you addressed safety only by descriptive statistics (i.e., proportions of each type of intra-operative and post-operative reportable event were compared between the study and control populations). In light of the fact that the patient follow-up rates were low, there is no way to know that the safety data presented is representative of the entire patient population. Therefore, any subsequent statistical analysis in which a comparison is made between the subject and control devices with respect to intra-operative and post-operative reportable events may contain patient selection bias.

However, if the following additional information is provided, as discussed in our meeting on March 29, 2001, we believe that you may be able to provide well documented case histories of each patient which may give a more complete picture of the safety and effectiveness of the Ascension MCP joint prosthesis as compared to a control than what has been presented in your PMA thus far. Please be advised that by addressing the following items, we are proposing one of several potential ways in which you may present your data to support the safety and effectiveness of the Ascension MCP joint prosthesis:

1. Although you provided a proposed list of indications for the Ascension MCP on p.15 and a list of inclusion/exclusion criteria for the pyrolytic carbon joint prostheses in this PMA on p.137, it appeared as if (1) the patients receiving pyrolytic carbon joint prostheses had very different baseline medical conditions; and/or (2) the physician had different goals for patients with different baseline medical conditions. For example:

   - Some patients would receive only one pyrolytic carbon joint prosthesis per hand while others would receive the pyrolytic carbon joint prosthesis in every joint in their hand;

   - In 6/53 patients (or 18/147 implants), the physician implanted one or more pyrolytic carbon joint prosthesis and one or more control devices in the same hand of the same patient but the reason for the selection of either a study or control device was not given;

   - A patient for whom a pyrolytic carbon implant was intended, received a control device because of a lack of collateral ligaments yet this condition was not listed as a contraindication for the Ascension MCP;

   - Twenty-two MCP joints in 11 patients had soft tissue procedures performed after receiving a pyrolytic carbon joint prosthesis to correct recurrent deformities such as ulnar deviation, flexion contracture, and subluxation and all but 1 joint in 1 patient involved patients with either rheumatoid arthritis or systemic lupus erythematosus;

   - Some patients entered the study without pain, loss of function, lack of strength, or deformity, yet these patients were all pooled together without adequate justification (e.g., 4/35 patients evaluated at baseline had no pain; 1/18 patients evaluated at baseline had unlimited function; some patients had pinch and grip strengths at baseline comparable to "normal patients" ("normal patient" strength defined in M990022/M001); and some patients had little or no ulnar deviation at baseline); and

   - The proximal component stem of 5 pyrolytic carbon implants in 3 patients had to be shortened at the time of surgery to prevent interference with prostheses used in prior

total wrist arthroplasty and 4/5 had to be subsequently removed yet this type of implant modification was not listed as a contraindication for the Ascension MCP.

Therefore, please:

a. Either stratify your study patient population by baseline medical conditions and physician expectations for each type of patient or justify poolability. You may find that for certain patient populations, the pyrolytic carbon joint prosthesis was successful while for other patient populations it was not. This type of information should inform your proposed indications for use, contraindications, warnings, etc. for the Ascension MCP;

b. Provide definitions for individual patient hand and finger joint success and failure with respect to device effectiveness for each group identified in item 1a including criteria for pain, function (finger joint and hand), and radiographic data;

c. Provide definitions for individual patient hand and finger joint success and failure with respect to device safety for each group identified in item 1a including criteria for intra-operative and post-operative reportable events such as fracture, subluxation, dislocation, re-operation, infection, loosening, etc.;

d. Evaluate each patient and determine if they are a success or failure in terms of safety and/or effectiveness based on your definitions from 1b and 1c;

e. Evaluate each group of patients identified in item 1a and determine the number of successes and failures;

f. Compare the results of your analysis with a control that has been matched for baseline medical conditions and physician expectations for device implantation to demonstrate that there is reasonable assurance of the safety and effectiveness of your device under its conditions of use; and

g. Provide copies of all referenced literature articles to support your response to items 1a, 1b, 1c, and 1f.

2. In our meeting on March 29, 2001, you stated that physicians are refusing to use the Swanson Silicone implants (and other constrained polymer MCP, hand, and wrist joint prostheses) for various reasons including:

- Reports of reactive synovitis in MCP from use of silicone implants;

- Silicone implants provide limited functional results for patients with advanced rheumatoid arthritis (RA) and this limits their use to salvage procedures;

- Silicone implants fracture, subside and provide limited motion for patients with osteoarthritis and traumatic arthritis; therefore, there is no currently available satisfactory prosthesis for these patients;

- In RA patients with pain, there is early subluxation and drift when silicone devices are used; therefore, these implants do not offer enough improvement in function to warrant surgical intervention and these patients are going without treatment; and

- Hand surgeons currently reserve arthroplasty for more severe disease and salvage because of the limited expectations with silicone devices.

Therefore, in order to provide a complete risk/benefit analysis for your device as compared to a control, please identify all risks associated with these types of implants and provide literature summaries and copies of any literature references used to support your statements.

3. As part of your response to item 1, please address the following:

a. Based on our analysis of the case histories summarized in Appendix A.6, 18/53 patients had less than 2 years worth of information about their pyrolytic carbon joint prostheses and for the following patients, you reported that they had more than 2 years worth of follow-up information (i.e. patients 6, 7, 10, 17, 18, 25, 31 and 48). Please clarify this apparent discrepancy. Please note that for total joint replacement devices, we typically request a minimum of 2 years of follow-up data on each patient before safety and effectiveness are evaluated;

b. Based on our review of Appendix 1 and Appendix A.6, there is an apparent discrepancy regarding whether or not patient 35 had the pyrolytic carbon joint prosthesis removed from her right index finger or not. Please clarify this apparent discrepancy;

c. On p.178, it appears as if patient 38 is mentioned incorrectly as having an implant fracture. Please clarify this apparent discrepancy;

d. On p.178, patients 26 and 43 were not included as patients who had pyrolytic carbon implants fracture. However, on pp.1492 and 1500, it appears as if there were fractures of pyrolytic carbon joint devices for patients #26 (right ring MCP joint) and #43 (right long) that were not intraoperative. Please clarify this

apparent discrepancy and discuss the circumstances with regard to these potential implant fractures;

e. On p.185, patient 49 was not included in the list of patients who experienced radiolucency around the pyrolytic carbon joint device. However, on pp.1501 and 1502, 2 lucency events were recorded for patient 49. Please clarify this apparent discrepancy;

f. On p.181, you reported 2 subluxation/dislocation events for patient 13 and 1 subluxation/dislocation event for patient 39. However, on p.1487 it appears as if patient 13 had 4 subluxation/dislocation events and on p.1497 it appears as if patient 39 had 2 subluxation/dislocation events. Please clarify this apparent discrepancy; and

g. On p.1497 in a note dated 8/6/84 for patient 39, you stated that there was "scattered histiocytes containing pigmented fine particulate matter." However, on p.340 in the Descriptive Pathology Narration, you reported that there was no foreign material. Please clarify this apparent discrepancy.

4. Regarding your secondary effectiveness endpoints, please provide the following:

a. A protocol for how the grip strength measurements were determined;

b. A protocol for how the pinch strength, oppositional and appositional, measurements were determined;

c. Please provide information, with literature support, for the accuracy and repeatability of the grip and pinch strength measurements.

5. On p.8 of Amendment 2, you provided a table of implant specific pain that appears to be misleading. It appears as if you used the numbers in the column titled, "N=patients" for the denominator when calculating the percentages in the column titled, "% w/out pain." However, from the information provided on p.157 of the original PMA submission and in Table 3 of Amendment 1, it appears as if the denominators should be much less due to loss to follow-up. Therefore, please clarify this apparent discrepancy by providing:

a. A revised table that identifies the number of patients without pain and the number of patients without information on pain; and

b. In light of the information requested in item 6a, recalculate the percentages of patients with and without pain and compare the results to the control.

The following additional minor deficiencies were noted in this initial scientific review and the indicated responses should be provided:

6. Please provide a revised surgical technique in which you discuss implant removal and summarize the potential problems associated with this procedure.

7. Please provide revised Summary of Safety and Effectiveness Data (SSED), package insert, patient and physician labeling that includes applicable information requested above.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

This letter reflects the current progress of our review of your application. Please be advised that further substantive review of your application or any response to this letter may result in additional deficiencies.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (20 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. Any additional information to be included in your PMA should be submitted in the form of a PMA amendment and be received by FDA at least 8 weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 4 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory panel meeting.

If you have any questions concerning this deficiency letter, please contact Mr. John S. Goode at (301) 594-2036 ext. 155.

Sincerely,

Daniel G. Schultz, M.D.
Deputy Director for Clinical and
Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health